

## Original Article

## The predictive value of FDG PET/CT in the evaluation of bone marrow involvement in lymphoma patients

### Lenfoma hastalarında kemik iliği tutulumunu değerlendirmede FDG PET/BT'nin prediktif değeri

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#### ABSTRACT

**Introduction:** The aim of the current study was to determine the role of PET-CT in the evaluation of bone marrow (BM) involvement during initial staging in patients with newly diagnosed lymphoma.

**Methods:** A retrospective analysis was made of 104 patients who were admitted to our Hematology Department between January 2010 and September 2016 and were diagnosed with lymphoma. Patients were classified as Hodgkin (HL) and Non-Hodgkin Lymphoma (NHL). NHL patients were evaluated in two subgroups as aggressive and indolent.

**Results:** The patients comprised 54 (51.9%) males and 50 (48.1%) females and were classified as 24 patients with HL and 80 with NHL. BM biopsy showed BM involvement in 40 patients (38.5%) and there was no pathological finding in 64 (61.5%) patients. BM involvement was detected on PET-CT in 41 (39.4%) of the whole patient group, of which 26 (63.4%) cases had diffuse infiltration and the remaining 15 (36.6%) cases had patchy infiltration. For all lymphoma patients, sensitivity of PET-CT was 80% and specificity was 85.9%. Sensitivity and specificity of PET-CT was 92.3% and 81.8% for HL patients and 74.1% and 86.8% for NHL patients, respectively. For only aggressive NHL patients, PET-CT sensitivity was 81.8% and specificity was 87.75%.

**Discussion and Conclusion:** PET-CT is an effective method for assessing BM involvement with a higher sensitivity especially for HL and aggressive NHL patients in detecting patchy involvement. The fact that it is non-invasive and easy to apply may support that it can be used instead of BM biopsy.

**Keywords:** Lymphoma, Bone Marrow Involvement, Biopsy, PET-CT

#### ÖZET

**Giriş ve Amaç:** Bu çalışmanın amacı, yeni tanı konmuş lenfoma hastalarında ilk evreleme sırasında kemik iliği (BM) tutulumunun değerlendirilmesinde PET-BT'nin rolünü belirlemektir.

**Yöntem ve Gereçler:** Ocak 2010-Eylül 2016 tarihleri arasında Hematoloji Bölümümüze başvuran ve lenfoma tanısı alan 104 hastanın retrospektif analizi yapıldı. Hastalar Hodgkin (HL) ve Hodgkin Dışı Lenfoma (HDL) olarak sınıflandırıldı. HDL hastaları da agresif ve yavaş seyirli olmak üzere iki alt grupta değerlendirildi.

**Bulgular:** Hastaların 54'ü (%51.9) erkek ve 50'si (%48.1) kadındı ve 24 HL'li ve 80 HDL olarak sınıflandırıldı. Kemik iliği (Kİ) biyopsisi 40 hastada (%38,5) Kİ tutulumu gösterdi ve 64 (%61,5) hastada patolojik bulgu görülmedi. PET-BT ile tüm hasta grubunun 41'inde (%39,4) Kİ tutulumu saptandı, bunların 26'sında (%63,4) yaygın infiltrasyon, kalan 15'inde (%36,6) yamalı infiltrasyon vardı. Tüm lenfoma hastaları için PET-BT'nin duyarlılığı %80 ve özgüllüğü %85.9'du. PET-BT'nin duyarlılığı ve özgüllüğü HL hastaları için sırasıyla %92,3 ve %81,8 ve NHL hastaları için %74,1 ve %86,8 idi. Sadece agresif HDL hastaları için PET-BT duyarlılığı%81.8 ve özgüllük% 87.75 idi.

**Tartışma ve Sonuç:** PET-BT, yamalı tutulumun saptanmasında özellikle HL ve agresif HDL hastalarında Kİ tutulumunu daha yüksek bir duyarlılıkla değerlendirmek için etkili bir yöntemdir. Non-invaziv ve uygulanmasının kolay olması BM biyopsisi yerine kullanılabileceğini destekleyebilir.

**Anahtar Kelimeler:** lenfoma, kemik iliği tutulumu, biyopsi, PET-BT

## Introduction

Lymphomas are clonal tumors originating from lymphocytes (T and B) or NK (natural killer) cells from immune system cells. They have different morphological, immunological and clinical features depending on the differentiation stage of the cell from which they originate [1]. The Ann-Arbor classification is used for lymphoma staging [2]. Correct staging is essential for effective treatment planning [3, 4]. While computed tomography (CT) is the most commonly used imaging method for initial staging in Non-hodgkin Lymphoma (NHL) patients, PET-CT, which combines positron emission tomography (PET) and computed tomography (CT), shows involvement more effectively than CT, especially in aggressive lymphomas. [5]. PET-CT is now the standard method for HL and aggressive NHL staging, but it has low diagnostic value in slow-progressive lymphomas [6, 7].

Bone marrow (BM) involvement is of great importance in the staging of lymphoma and thus in determining treatment and prognosis. [8]. BM involvement is present in approximately 25-40% of NHLs and 5-14% of HLs [9, 10]. Unilateral BM biopsy of the dorsal iliac crest is accepted as the gold standard in routine evaluation of BM involvement and is routinely performed [2]. However, it has some limitations such as being an invasive painful procedure and bypassing limited involvement. PET-CT has been evaluated as useful in demonstrating BM involvement in various studies [3, 4, 11, 12], and has therefore been accepted as a complementary study for BM biopsy [13, 14].

The aim of the current study is to determine the predictive value of PET-CT in comparison with BM biopsy results in the evaluation of BM involvement in HL and NHL patients.

## Patients and methods

This study included 24 HL and 80 NHL patients admitted to Necmettin Erbakan University Hematology Department between January 2010 and September 2016 who were diagnosed with HL and NHL. All patients underwent both PET-CT and BM biopsy for initial staging. In the clinical staging, physical examination, laboratory tests, PET-CT results, and unilateral BM biopsy results were recorded. Stage, presence of B symptoms, histopathological diagnosis and demographic information were obtained from patient files. The PET-CT findings of the patients were re-evaluated and recorded with SUV (Standardized Uptake Value) max measurements from the right lobe mid-segment segment 7-8, spleen parenchyma and dorsal iliac wing region where BM biopsy was performed. Spleen parenchyma and BM areas with a higher SUVmax measurement than liver parenchyma were accepted as involvement. Cases with increased diffuse bone marrow activity in PET-CT were evaluated as involvement and recorded. Cases with irregular, non-diffuse increase in metabolic activity were defined as patchy BM involvement and recorded. BM biopsy was accepted as the gold standard in demonstrating involvement, and sensitivity-specificity tables were made according to the results of biopsy and PET-CT. According to these tables, the sensitivity, specificity, positive and negative predictive values of PET-CT in demonstrating BM involvement were calculated.

## Statistical Analysis

Statistical analysis was performed using SPSS version 16 software and Excel 2013. The conformity of the variables to normal distribution was examined with the Kolmogorov Smirnov and Shapiro-Wilk tests. Data with normal distribution were presented

as mean  $\pm$  standard deviation, and data without normal distribution as median (minimum - maximum) values.

#### Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval for this cross sectional study was granted by Necmettin Erbakan University Faculty of Medicine Ethics Committee (Number: 2016/680 Date: 30.09.2016)

### Results

#### All patients

Twenty four HL and 80 NHL patients were included in the study. The most common subtypes were Nodular Sclerosis among HL (n=17, 16.3%) and Diffuse Large B Cell Lymphoma (n=56, 53.8%) among NHL patients. All subtypes are shown in Table 1. The patients comprised 54 (51.9%) males and 50 (48.1%) females with a median age of 60.5 years (range, 20-90 years). Advanced stage disease was present in 75 patients (72.2%) and 47 patients (45.2%) had B symptoms at the time of diagnosis. The total mortality rate was 24% (n=25) at the final follow-up time. The demographic and disease characteristics are shown in Table 2.

The BM biopsy results revealed that 40 patients (38.5%) had involvement and 64 patients (61.5%) had no involvement. BM involvement was detected on PET-CT in 41 (39.4%) of all patients, 26 (63.4%) of which were diffuse and the remaining 15 (36.6%) were patchy (Table 3). The sensitivity and specificity of PET-CT were 80% and 85.9%, respectively. The positive predictive value (PPV) of PET-CT in the assessment of BM involvement was 78% and the negative predictive value (NPV) was 87.3% (Table 3).

#### HL patients

Twenty four HL patients with a median age of 46 years [range, 20-70 years] were evaluated

(Table 2). BM biopsy showed involvement in 13 (54.2%) patients and no involvement in 11 (45.8%) patients. On PET-CT, BM involvement was detected in 14 (58.3%) patients and no involvement in 10 (41.7%) patients. Of these involvements, two (14.3%) were patchy, and 12 (85.7%) showed diffuse involvement. The demographic and disease characteristics and BM involvement results of HL patients are shown in Table 2. In HL patients, the PET-CT sensitivity to BM involvement was 92.3% and specificity was 81.8%. The PPV of PET-CT was 85.7% and the NPV was 90% in HL patients (Table 3).

#### NHL patients

Eighty (76.9%) NHL patients with a median age of 64 [range, 21-90 years] were evaluated (Table 2) BM biopsy revealed involvement in 27 (33.7%) patients, and no involvement in 53 (66.3%) patients. On PET-CT, BM involvement was not detected in 53 (66.3%) patients and was observed in the remaining 27 (33.7%) patients. Of these, 13 (48.1%) were patchy and 14 (51.9%) had diffuse involvement. The demographic and disease characteristics and BM involvement results of NHL patients are shown in Table 2. The sensitivity of PET-CT for detecting BM involvement in NHL patients was 74.1% and specificity was 86.8%. PET-CT had a PPV of 74.1% and a NPV of 86.8% (Table 3).

In the evaluation of 71 aggressive NHL patients, BM biopsy showed involvement in 22 (31.0%) patients and 49 (69.0%) patients had no BM involvement. On PET-CT, 24 (33.8%) patients had involvement while 47 (66.2%) patients had no involvement (Table 3). The sensitivity and specificity of PET-CT for aggressive NHL patients was 81.8% and 87.75%, respectively. The PPV of PET-CT was 75% and the NPV was 91.5%.

In the evaluation of 9 NHL patients with an indolent course, 5 (55.6%) patients had involvement in the BM biopsy, and 4 (44.4%) patients had no involvement. When evaluated with PET-CT, involvement was observed in 3 (33.3%) patients and no involvement was observed in 6 (66.7%) patients.

Table 1. Diagnostic subgroups of the patients

Diagnosis	Subgroup	n (%)
Hodgkin Lymphoma	Nodular Sclerosis HL	17 (%16,3)
	Lymphocyte Rich HL	3 (%2,9)
	Mixed Cellularity HL	3 (%2,9)
	Lymphocyte Depleted HL	1 (%1)
Non-Hodgkin Lymphoma	Diffuse Large B-cell Lymphoma	56 (%53,8)
	Mantle cell Lymphoma	5 (%4,8)
	Peripheral T-cell lymphoma	5 (%4,8)
	Angioimmunoblastic T cell lymphoma	2 (%1,9)
	Anaplastic large cell lymphoma	2 (%1,9)
	Marginal Zone Lymphoma	6 (%5,8)
	Follicular lymphoma grade I and II	2 (%1,9)
	Follicular Lymphoma Grade III	1 (%1)
Small Lymphocytic Lymphoma	1 (%1)	
All		104 (100)

Table 2. General Demographic Findings and Bone Marrow Involvement

	HL (N=24)	NHL (N=80)	All (N=104)
Age Median [min-max.]	46.0 [20-70]	64 [21-90]	60.5 [20-90]
Gender			
Male	12 (%50,0)	38 (%47,5)	50 (%48,1)
Female	12 (%50,0)	42 (%52,5)	54 (%51,9)
Stage and B symptoms			
I / IB	1(4,2%) / 1(100%)	7(%8,8) / 0(0%)	8 (%7,7) / 1(12,5%)
II / IIB	5(20,8%) / 2(40%)	16(20,0%) / 7(43,7%)	21 (20,2%) / 9(42,8%)
III / IIIB	5(20,8%) / 1(20%)	30(37,5%) / 16(53,3%)	35(33,7%) / 17(48,5%)
IV / IVB	13(54,2%) / 8(61,5%)	27(33,7%) / 12(44,4%)	40(%38,5) / 20(50%)
BM Involvement in PET-CT (n)			
Patchy	2 (8,3%)	13 (16,2%)	15 (14,4%)
Diffuse	12 (50,0%)	14 (17,5%)	26 (25,0%)
Patients' survival			
Survivors	22 (91,7%)	57 (71,3%)	79 (76,0%)
Nonsurvivors	2 (8,3%)	23 (28,7%)	25 (24,0%)

HL: Hodgkin lymphoma, NHL: Non-Hodgkin lymphoma, BM: Bone marrow

Table 3.1 Evaluation of bone marrow involvement in all patients

	Overall (n=104)		HL (n=24)		NHL (n=80)	
	BMB (+)	BMB (-)	BMB (+)	BMB (-)	BMB (+)	BMB (-)
PET CT (+)	32	9	12	2	20	7
PET CT (-)	8	55	1	9	7	46
Total	40	64	13	11	27	53

BMB: Bone marrow biopsy, HL: Hodgkin lymphoma, NHL: Non-Hodgkin lymphoma

## Discussion

Correct staging of the disease is of great importance in follow-up and survival in patients with lymphoma [3, 4]. PET with radioactive fluorine-18-labeled glucose analogue 18F-Fluorodeoxyglucose (FDG) is increasingly used in the evaluation of various malignant tumors, including lymphoma. [15-18]. The most important advantage of PET-CT is the ability to distinguish between active tumoral tissue and necrosis and fibrosis [19-21]. Anemia, infections, G-CSF use, chemotherapy (CT) use that may cause bone marrow activation during PET-CT scan may cause false positives but do not exclude BM involvement. [4, 22].

BM biopsy is the gold standard method for BM involvement. However, it is an invasive method and there are also some difficulties in achieving certain standards in terms of efficiency during implementation. According to a study by Brain, the minimum length of the biopsy material was determined as 16 mm [23], while 20mm was the minimum length of unilateral biopsy required by Campbell et al [24]. As this procedure is quite painful and it is difficult to obtain adequate sampling, the search for other non-invasive tests has increased. In many studies, it has been shown that PET-CT and BM biopsy are compatible with BM biopsy results, which is the most important step in the staging of lymphoma patients. In the current study, the correlation between PET-CT and patients with BM involvement was 80%. These results were found to be compatible with the 78% and 80% correlation reported by Carr et al. and Pakos et al., respectively [8, 25].

In the current study, lymphoma patients were evaluated under the headings of HL and NHL, and the NHL patients were further analyzed as aggressive or indolent. Previous studies have reported that BM involvement is seen in 5-14% of HL [26] and 30-50% of NHL [27, 28], whereas when the subgroups are evaluated, BM involvement is seen in 18-36% of aggressive NHL and in 40-90% of indolent NHL [29]. In the current study, BM involvement was found in 54.2% of the HL

patients, which was a higher rate than in recent reports in literature. Such a difference may have occurred because the number of HL patients included in this study was low. In the NHL patients, BM involvement was found in 33.7%, which was a similar rate to those previously reported. According to the subgroup evaluation, BM involvement was seen in 31% of the aggressive NHL group and in 55.6% of the indolent NHL group.

In the current study, BM biopsy detected involvement in eight patients where PET-CT showed no involvement. Of these 8 patients, one was HL, four were aggressive NHL and three were indolent NHL. Previous studies have shown that PET-CT has very low sensitivity to show BM involvement in Mantle Cell Lymphoma with low FDG uptake regardless of aggressive or indolent NHL grouping [14]. In the current study, three patients were followed up with the diagnosis of indolent group NHL and two patients with Mantle Cell Lymphoma. However, BM involvement can be missed on PET-CT in lymphomas with low density (10-20%) [30]. This may have been the cause of inconsistency in the remaining 3 patients.

In nine patients, BM involvement was determined with PET-CT while BM biopsy revealed no involvement. Of these patients, two were HL, 6 were aggressive NHL and one was indolent NHL. In recent studies, it has been reported that BM involvement may be in a diffuse pattern or it may exhibit patchy involvement [31, 32]. In the absence of FDG uptake in the biopsy area, involvement in BM biopsy may not be observed. In the current study, patchy involvement was observed in four patients who had no involvement on BM biopsy but had PET-CT involvement and the SUVmax values in the posterior iliac wing region were found to be relatively low. Although obtained in accordance with the literature, it is thought that the biopsy material of the remaining 5 patients who did not show involvement in BM biopsy was not sufficient for definitive diagnosis. [33-35]. It has been reported in another study that even if sufficient and bilateral biopsy was performed,

accuracy could only be increased by 10-50%. [25].

In a meta-analysis by Pakos et al., which discussed the role of PET-CT in demonstrating BM involvement in 13 studies with 587 patients, the sensitivity and specificity for detecting BM involvement were evaluated as 51% and 91%, respectively. It was shown that half of 12 patients who had BM involvement on PET-CT but not on biopsy showed BM involvement when the BM biopsy was repeated. [25]. Muslimani et al. reported PET-CT sensitivity as 79% and specificity as 91%. Sensitivity and specificity rates were lower in the NHL group, but there was no statistically significant difference [36].

In the current study, when all the patients were evaluated, sensitivity was found to be 80%, specificity 85.9%, PPV 78%, and NPV 87.3%. When the subgroups were evaluated, the highest sensitivity was 92.3% in HL patients. According to these results, PET-CT to show BM involvement; they are an effective method for HL patients and less effective for NHL patients. When sensitivity

and selectivity were evaluated for the NHL subgroups, PET-CT appears to be more effective in the evaluation of BM involvement in aggressive NHL patients than in all NHL patients and indolent NHL patients.

### Conclusion

In the evaluation of BM involvement in lymphoma patients, PET-CT is a very useful but not perfect method. Although it is a non-invasive method, the increase in cost should also be considered. In order to evaluate BM involvement effectively, BM biopsy can be performed after PET-CT, especially for the determination of BM involvement in lymphomas with patchy involvement. The efficacy of PET-CT in HL and aggressive NHL patients is quite high, and although there is still no substitute for BM biopsy, these methods complement each other. As PET-CT activity is low in indolent lymphomas, it cannot replace biopsy. Further larger patient-based studies are needed to evaluate the value of PET-CT for BM involvement instead of biopsy.

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